Non-invasive blood testing in epistaxis

A prospective pilot study comparing nasal blood sampling and venipuncture for the assessment of haemoglobin levels and INR

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Level of Evidence: 4

ABSTRACT

Background: This study is a pilot study evaluating the feasibility of sampling nose-blood during an emergency using a commercially available rapid test device. It also compares the accuracy of rapid nasal blood test results to the results of standard laboratory methods using venous blood sampling.

Methodology: Nose-blood was collected in patients suffering from active epistaxis. In an emergency setting, haemoglobin levels and the international normalized ratio (INR) were assessed using a rapid point-of-care test device. These results were compared to standard laboratory analyses from venous blood taken at the same time from the same patient. Twenty patients consented to and participated in these assessments.

Results: Linear regression comparing venous and nasal samples revealed strong correlations between the two methods for both haemoglobin and INR measurement. A Bland-Altman analysis showed the mean difference to be 2.3 g/l when comparing haemoglobin measurements made using the rapid point-of-care device to haemoglobin measurements made using conventional lab assessment. The corresponding mean difference for INR measurements was 0.14.

Conclusions: The results of this pilot study support the use of point-of-care test devices using nasal blood sampling and provide preliminary data demonstrating that a rapid testing method can be reliable, practicable and time-efficient. In our opinion rapid hematologic screening for nasal and capillary blood should be available in emergency wards which treat epistaxis.

INTRODUCTION

The treatment of epistaxis (nosebleed) is routine for otolaryngologists, emergency specialists and general practitioners. More than half of all adults have had or will experience an episode of nosebleed[1]. This is often harmless and self-limiting, and may be managed by the patient. Nevertheless, severe cases require medical attention and may potentially lead to relevant and measurable blood loss. Anaemia due to epistaxis can usually be attributed either to a single episode being particularly severe or due to recurring bleeding[2].

In anticoagulated patients, management algorithms incorporating lab haematology findings play a decisive role. Of the lab values that haematology tests deliver, Hb (haemoglobin) often serves physicians as a threshold indicator for the initiation or adaptation of therapy. For example, blood transfusions are given if Hb is low, Hb levels help determine whether or not vitamin K substitution is necessary in a severely anticoagulated patient, and the removal of nasal packs in high risk patients with anaemic Hb levels should be prolonged for another 24 hours[3].

Though routine laboratory screening is considered useful or even recommended for the paediatric population[4, 5], similar lab screening for anaemia or coagulopathies is not recommended in otherwise healthy epistaxis patients[6]. The decision to evaluate Hb and INR during an emergency is instead based upon the patient's history, the resources available in the particular emergency setting, and it takes into account clinic or medical system specific economic considerations. Indeed, the gold standard for hematologic testing, namely venous puncture and blood sampling involving laboratory analysis, is time consuming and acutely ties up medical staff. Furthermore, it is painful for the patient and generates financial expenses. It is possible direct sampling could avoid many of these inconveniences, at least in cases of epistaxis. Direct, rapid-test sampling of the nasal blood could effectively mitigate the inherent pathologic mischief of the nosebleed by providing clinicians the opportunity to exploit the fact that patient is already bleeding to diagnostic and health-economic advantage.

Commercially available, rapid test devices for capillary blood analyses exist. By making use of one, it is possible the workload for doctors and medical/hospital staff, caused by high volumes of epistaxis patients and it's time-consuming routine therapeutic and diagnostic procedures, could be reduced, that time and expense could be saved, and pain on the part of the patient could be avoided. Furthermore, the clinical and economical threshold for acquiring valuable hematologic information could conceivably be lowered. The dual aims of this pilot study were a) to evaluate the clinical feasibility of sampling relatively impure nose-blood using two commercially available rapid test devices, and b) to compare the reliability of the rapid-test devices to standard venous blood sampling involving lab analysis.

MATERIALS AND METHODS

This investigation was designed as a prospective pilot study at the University Hospital of Zurich. Between March 2015 and June 2015 we collected blood samples from 20 epistaxis patients. Patients suffering from active nosebleed of a sufficient volume were included in the study during their treatment at the university hospital's ENT emergency ward. After briefly orienting a patient regarding the study and securing definitive oral consent, we immediately initiated treatment. After primary treatment, we repeated the informed consent process for the sake of verification, this time without the stress of the nosebleed and its treatment, and obtained formal written consent. We collected data regarding the patient's demographic details, any history of antithrombotic medication, the localization of the bleed site (i.e. the specific nasal location), the INR and Hb values using nasal blood, and the INR and Hb values as collected via standard venous-blood harvesting methods (analysed in the hospital's diagnostic lab).

To avoid dilution of the nasal blood, we did not apply local anaesthesia or vasoconstrictive agents before collecting nasal blood samples. Two to three drops of nose-blood were caught directly on the INR test strip of the "Roche CoaguChek XS Plus®" rapid-testing device. We transferred some of the blood from this relatively 'big' drop to a Hb test strip using a microcuvette (HemoCue Hb 201+®). The standard venous blood sample was taken a few minutes after treatment of the bleed and sent to the university hospital's on-site laboratory for evaluation. The outputs of the two rapid devices, namely Hb in grams per litre and INR in per cent, were compared to the results of the standard lab testing procedure.

The statistical analyses and charts were conducted using the Statistical Package for the Social Sciences software package (SPSS), Version 22.0.0.1 (IBM Corp., Armonk, NY, USA). The data were analysed for agreement using a method described by Bland and Altman[7] in which graphs are used to compare the differences of individual measurements to a mean difference.

The study was conducted in accordance with the latest version of the Helsinki declarations

and with the permission of canton Zurich's ethics committee (KEK-ZH-Nr.: 2014-0679, ClinicalTrials.gov-Identifier: NCT02370381). It was investigator initiated and financed by University Hospital Zurich's ENT department. The HemoCue Hb 201+® device was provided on loan and cuvettes were offered free of charge by an independent local distributor. The Roche CoaguChek XS Plus® device was already part of our emergency equipment.

RESULTS

Twenty patients provided written informed consent following initial oral consent and emergency treatment and were included in this study. None of the patients approached to participate withdrew the initial oral consent they had given prior to receiving treatment.

The cohort included 14 (70%) male and 6 (30%) female patients. The mean age of the patients at the time of epistaxis treatment was 64.4 years (SD 18.9 [24.6 – 89.2 years]). An anterior nasal bleed location was the most commonly observed location, seen in 75% (15) of the population. Sixty-five percent of the patients reported prior intake of haemostasis impairing medication. This included 8 (40%) patients who had taken only acetylsalicylic acid (ASA), 1 (5%) patient who took ASA in conjunction with other medications, and 3 (15%) patients who had had only a vitamin K antagonist (VKA). One patient was known to suffer from hereditary haemorrhagic telangiectasia.

The mean Hb level measured in venous blood was 140 g/l [range 95-167 g/l]. The average nasal blood Hb level was 138 g/l [range 88-179 g/l]. Linear regression comparing Hb values derived using conventional venous puncture as the dependent variable and nose-blood Hb as an independent variable demonstrated a positive correlation ($r=0.85$; $p<0.01$). Figure 1. Bland-Altman analysis showed that the average observed difference between measurements taken using the two test-types was 2.3 g/l with a 95% confidence interval (CI) - 20.8 g/l to 25.4 g/l. On average, this is slightly less than a 2% difference separating the measures delivered by rapid nasal blood testing and venous blood lab testing. Figure 2. This small difference would seem clinically irrelevant, and a one-sample t-test demonstrated that this average difference is indeed statistically insignificant (reference value 0). This suggests that the measurement discrepancies between the two test modalities (on average around 2.3 g/l) are irrelevant. The lack of linear correlation between the difference of values and the mean difference confirmed that no proportional bias was present ($p=0.1$). There were two outliers outside the 95% CI. In one case Hb was overestimated in the nasal sample by 23 g/l. In

another patient it was underestimated by 40 g/l. These outlying values would not, however, have altered the course of treatment or a decision to provide a blood transfusion.

The mean INR value measured in our patient's venous blood was 1.2 [range 1-3.3]. For nasal blood the comparable mean value was 1.3 [range 0.8-2.2]. Figure 3. Again, linear regression using venous puncture INR as the dependent variable and nose-blood INR as an independent variable demonstrated a significant correlation ($r=0.86$, $p<0.01$). The mean difference between measurements was 0.14 [95% CI -0.5;0.8] was demonstrably not significant (one sample T-test $p=0.08$). However, there was a positive correlation between the mean difference and the mean value of the two measurements. This suggests that higher values have a higher risk of bias. For these sample sets two outliers were observed (95% CI): In one case nasal INR was 1.3 lower than the INR of the corresponding venous sample. In the second case the nasal sample measurement was 0.6 greater than the venous measurement. In the latter case, the patient was ultimately determined to have a normal INR, and we noted that this was the same patient for which a low-lying nasal blood Hb outlier value had been observed (an apparent undervaluation of the true Hb value).

DISCUSSION

Our study shows the feasibility, cost effectiveness and accuracy of sampling nasal blood for the analysis of haemoglobin and INR values using point of care devices in epistaxis.

Hb and INR testing are amongst the most commonly performed blood tests in an epistaxis emergency setting. Time-intensive analyses usually have a naturally high threshold, impeding their initiation and often avoided in the midst of a clinical emergency. Indeed, when treating epistaxis at the emergency ward, it is fairly likely, that after the usually short treatment the patient has to wait another hour just for the lab results to arrive. Especially for cases with a high probability for anaemia, an Hb level has to be acquired before the patient can be discharged.

The additional expenditure of cost and time has led to the general consensus that routine assessment of blood values in an epistaxis emergency is not considered to be a staple of general practice[4]. In an earlier investigation conducted at the Zurich University Hospital, high-risk transfusion cohorts were identified and characterized without the contemplation of blood values. The acronym THREAT (Trauma, Hematologic disorder, and REAr origin of bleeding) helps to remember and identify the factors associated with an increased risk of receiving blood transfusion[8]. Recent studies and growing recognition in the field of otolaryngology suggest that increased access to INR and Hb levels in epistaxis patients could be beneficial and worth recommending in specific patient populations.

A work examining a population of paediatric epistaxis patients revealed a 22% rate of anaemia and a 7.8% rate of bleeding disorders[5]. This study group has gone so far as to propose routine screening of all paediatric epistaxis patients for anaemia and coagulopathies. Screening this population would prevent to leave many at-risk children untreated, and prone to the potentially harmful long-term consequences, at the costs of a painful blood sample.

More than a third of patients on vitamin K antagonists are outside of the INR target range in the setting of epistaxis[9, 10]. Thus, it would seem epistaxis is an apparent indicator of a

possible overexposure to antithrombotic medication, and testing to confirm this suspicion shouldn't be forgone. The consequences of not doing so, and the resultant overtreatment or undertreatment with blood thinners has been shown to lead to higher mortality[11].

Rapid test devices strain healthcare budgets much less than expenses generated via traditional laboratory analyses. Based on Swiss market prices, a single rapid Hb micro-cuvette costs 1 Swiss Franc (CHF). This equates to approximately 1 US Dollar (USD) at the current exchange rate (Jan. 2016). In comparison, the current cost of lab testing at our institution is nine times higher, 9 CHF (approx. 9 USD). Further increasing the costs, our in-house laboratory measures Hb using a hemogram, which unavoidably also assesses hematologic parameters beyond what is needed. A similar cost-imbalance exists for the INR testing, with rapid testing costing 3.5 CHF vs 6 CHF for conventional lab testing. The calculations presented here are admittedly basic. Many peripheral and non-material costs are not being fully considered, both for conventional venous blood testing, as well as for rapid nasal blood testing. These costs include but are not limited to the material for venipuncture sampling, transport to the lab, personell costs, and other intangibles. The acquisition of a rapid test device amounts to less than 1000 CHF. Maintenance and quality controls can easily be conducted without any professional knowledge by the user.

Obvious limitations apply to it, as patients without active bleeding are not amenable to nasal blood testing. Often these patients transition to an active nasal drip after intranasal manipulation during the treatment. Pragmatically, if nasal blood isn't available during treatment, the same devices could of course be used for capillary tests. This raises the issue, of course, that these rapid testing devices were not designed with nasal blood testing explicitly in mind. A reliable validation of these devices' applicability for use with nasal blood requires a larger scale study.

It's important to note, however, that the reasons nasal blood Hb and INR measurements occasionally deviate from venous sampling values remain unclear. Dilution prior to sampling

could be the cause for high INR and low Hb levels. Beyond this, it is possible that the enzymatic activity of nasal secretions might also bias measurements. The proteins present in these secretions could potentially lead to haemolysis and degradation.

Although our study, a pilot study, has a relatively small sample size (n = 20), the nasal Hb levels we observed were strikingly in-line with values delivered by conventional means. The accuracy of our Hb results using rapid test devices for nasal blood is well comparable to the accuracy when matching capillary with venipuncture testing[12, 13]. Also, our INR testing results for nasal blood were quite comparable to those reported by other studies comparing the merits of capillary blood testing to conventional venous testing[14]. Indeed the limits of agreement for INR were even narrower in our results. A positive proportional bias with greater differences for INR values at a higher range was also observed. The differences between nasal and conventional blood testing were ultimately clinically irrelevant and even the outliers mentioned wouldn't have had a negative effect on treatment or the indication for transfusion. Indeed, the observed deviations from rapidly sampled nasal blood resulted in Hb underestimation and INR overestimation. Thus, it is actually less likely that a rapid test device would fail to report a critically low Hb or a critically high INR level, keeping in mind that these types of errors are less dangerous for the patient than the other way around.

CONCLUSION

Our pilot study demonstrates the feasibility, reliability and the utility of conducting Hb and INR testing noninvasively using nose-blood in epistaxis patients and a point-of-care rapid test method.

Furthermore, it highlights the possible advantages that rapid testing may have over conventional venipuncture. Nasal blood testing could represent an easy, fast, painless and cost saving type of Hb and INR measurement. In emergencies, rapid course of action is paramount in order to make the right decisions and to improve the patient's outcome.

In our opinion rapid hematologic screening for nasal and capillary blood should be available in emergency wards which treat epistaxis.

ADDENDUM

Rafael R. Stadler obtained the consent of the local ethic committee, performed the patient enrolment, performed the data collection, analysed the raw data and prepared the manuscript. Michael B. Soyka has planned, supervised and designed the study. Acting as the principal investigator he helped with the analysis, prepared and reviewed the manuscript.

Nicolas Newcomb - from the Institute of Evolutionary Medicine, University of Zurich UZH, Zurich Switzerland - edited the manuscript.

FIGURE LEGENDS

Figure 1: Linear Model comparing the level of haemoglobin. The level of haemoglobin on the x-axis was measured from a venous puncture by the laboratory in g/l and the level of Hb on the y-axis was measured from nose-blood by the rapid test device in g/l.

Figure 2: Bland-Altman plot showing the differences between the HbLab (laboratory) and HbNose (rapid test device) in g/l plotted against the mean value of both measurements in the same patient. The horizontal lines mark the 95% confidence limit.

Figure 3: The differences between the INRLab (laboratory) and INRNose (rapid test device) in % are shown at the mean level of both measurements (Bland-Altman plot) of each patient. The horizontal lines mark the 95% confidence limit.

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